II. REMARKS

Status Summary

Claims 16 and 23-36 are pending and subject to the advisory action mailed August 8, 2007. Claims 1-15 and 17-22 were canceled previously. Claims 37-38 are new. Claims 25, 33 and 35 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 16 and 23-36 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Reconsideration and allowance of the present application based upon the following remarks are respectfully requested.

Preliminary Remarks

Claims 37-38 are newly added to define particular aspects of the invention. Claims 37 and 38 are directed to the method of claims 16 or 29, respectively, wherein the immunoconjugate or fusion protein, respectively, is administered to the subject by inhalation or transdermally. Support for the specified modes of delivery is found in the specification as originally filed on pages 22-23, bridging paragraph.

Abstracts Originally Submitted June 12, 2007

The following remarks again refer to abstracts of journal articles, which were originally submitted with the applicant's response filed June 12, 2007. The requisite fee for consideration of the cited abstracts was paid at the time of the applicant's prior response (June 12, 2007). As the fee for consideration of the cited abstracts was previously paid, the applicants believe that no such fee is now due and thus request that the examiner acknowledge that the cited abstracts have been considered.

Patentability Remarks

35 U.S.C. §112, first paragraph, written description

Claims 25, 33, and 35 were previously rejected as allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph, *see* official action, page 3, issued December 27, 2006. Specifically, the examiner states that the term "tositumomab"

encompasses an unlabeled antibody, which is allegedly unsupported in the instant application, *see* official action, page 3, December 27, 2006. In particular, the examiner alleges that the reference to Liu et al. (1998) regarding anti-B1 antibodies indicates that unlabeled antibodies are not supported by the specification. The examiner states that Liu et al. only describes using the iodine-131-labeled form of anti-B1 antibody to treat relapsed B-cell lymphoma patients.

The advisory action of August 8, 2007, fails to address the applicants' previous remarks regarding this rejection. Accordingly, the applicants reiterate that for the following reasons, the present specification supports the term "tositumomab."

The applicants respectfully submit that one of skill in the art at the time of filing would clearly understand that the reference on page 3 of the specification to "anti-B1 antibody" refers to unlabeled anti-B1 antibody. At the time the application was filed, unlabeled anti-B1 antibody (tositumomab) was known to have therapeutic B cell-depleting activity (*e.g.*, *see* Shan *et al.*, *Cancer Immunol. Therapy*, 2000, 48:673-83, abstract previously enclosed), and was routinely administered in combination with the iodine-131-labeled form of anti-B1 antibody in the treatment of B cell lymphoma. For example, *see* Koral *et al.*, *Cancer Biother. Radiopharm.*, 2000, 15:347-55; Vose *et al.*, 2000, *J. Clin. Oncol.* 18:1316-23; and Torizuka *et al.*, *J. Nucl. Med.*, 2000, 41:999-1005 (abstracts previously enclosed). Moreover, in these and other scientific articles published at the time of filing, the radiolabeled form of anti-B1 antibody is clearly identified as "iodine-131-anti-B1 antibody" or "iodine-131-tositumomab." The above-cited references show that, at the time of filing, persons of skill in the art commonly used the term tositumomab in published scientific articles to refer to unlabeled anti-B1 antibody. Nothing in the published literature suggests that reference to "anti-B1 antibody" actually means iodine-131-anti-B1 antibody. Accordingly, one of skill in the art would have understood the reference to "anti-B1 antibody" on page 3 of the present specification and in Lieu et al. (1998) to refer to unlabeled anti-B1 antibody (tositumomab), and would have considered the applicants to be in possession of the invention of claims 25, 33 and 35 at the time the application was filed. Withdrawal of the rejection of claims 25, 33, and 35 under 35 U.S.C. §112, first paragraph, for lack of written description is therefore respectfully requested.

35 U.S.C. §112, first paragraph, enablement

Claims 16 and 23-36 are rejected as allegedly failing to comply with the enablement requirement. In support of the rejection, the examiner refers to Davis *et al.*, *Clinical Cancer Research*, 2000, 6: 2644-2652, which the examiner states represents the state of the art using an immunoconjugate of anti-CD20 linked to IFN-α-2a. *See* advisory action, August 8, 2007. Davis *et al.* teaches that combination therapy with rituximab and IFN-α-2a in patients is effective at IFN-α-2a dosages of 2.5 or 5 million units administered three times weekly for 12 weeks, *see* advisory action, August 8, 2007. The examiner further cites the applicants' remarks of October 19, 2006, which states that the number of molecules of IFN-α-2a administered in the Davis study is 1,600 fold less than the dosage of anti-CD20 antibodies, *see* advisory action, August 8, 2007. Accordingly, the examiner alleges that the prior art does not provide adequate guidance as to the dosage of the instantly described immunoconjugate that is effective to kill B cell lymphoma cells or to treat B cell lymphoma. *See* advisory action, August 8, 2007. The examiner further alleges that the present specification fails to provide such guidance, and concludes that undue experimentation is required to practice the instant invention. *See* advisory action, August 8, 2007

In order to establish a *prima facie* case of non-enablement, the examiner must explain why the specification is not enabled based on sound scientific reasoning or acceptable evidence, which is inconsistent with statements in the specification asserting enablement. (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971). The applicants submit that the examiner has not met this burden.

The examiner relies in part on the "Wands Factors" in rejecting the claims for lack of enablement and focuses the basis of his rejection almost entirely on the factor of whether undue experimentation is required to practice the invention as claimed. In regards to undue experimentation, the court stated

> [t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* [48 F. 2d 872, 878-79;169 USPQ 759, 762-63 (2d Cir. 1971), *cert. denied*, 404 U.S. 1018 [172 USPQ 257] (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with

respect to the direction in which the experimentation should proceed." *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, the examiner fails to establish that the state of the art is insufficient to enable a skilled artisan to use the immunoconjugates described in the present claims. The examiner relies on Davis *et al.* to assert that undue experimentation is necessary to practice the invention. The examiner bases this assertion on the effective dose of the combination treatment of IFN-α-2a and anti-CD20 antibody described in Davis *et al.* Davis *et al.* describe a dosage of IFN-α-2a that is 1,600 fold less than that of the anti-CD20 antibody. As discussed in the response of October 19, 2006, this dosage would have, *inter alia*, deterred a skilled artisan from reasonably predicting that the instant immunoconjugates would have exhibited pharmacological activities comparable to the separately administered proteins described in Davis *et al.* Nevertheless, the Davis *et al.* reference does not address the experimentation required to determine the effective dose of the immunoconjugates as described in the claims and, accordingly, does not establish a *prima facie* case of non-enablement.

The applicants submit that the amount of experimentation that would be required to determine a therapeutically effective amount of the instant immunoconjugates would not be undue and would be considered reasonable and expected in the field of art. A skilled artisan was well-aware of the routine *in vitro* and *in vivo* methodologies used to establish effective doses of compounds including immunoconjugates, *see, e.g.*, bridging paragraph pages 13-14 in the specification as originally filed, which describes an *in vitro* screening assay used to determine therapeutic dosages. A skilled artisan was also well-aware that a precise dose to be employed in the treatment of B cell lymphoma depends on the disease stage, age, sex, medical complications and weight of the individual to be treated (*see e.g.*, page 7, paragraph 76 in the specification as-filed). Accordingly, the determination of an effective dose of the described immunoconjugates for the treatment of B cell lymphoma was routine for a skilled artisan.

Based on the foregoing, the applicants submit that the examiner has failed to establish any reasonable basis to question the enablement of the claimed methods. Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Double patenting

On page 5 of the official action issued December 27, 2006, the examiner objects to claim 35 under 37 C.F.R. §1.75 as allegedly being a duplicate of claim 33. The applicants acknowledge that the examiner has withdrawn this rejection. *See* advisory action, August 8, 2007.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
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